DOCTORAL CANDIDATE:	Sissel Hauge
DEGREE:	Philosophiae Doctor
FACULTY:	Faculty of Mathematics and Natural Sciences
DEPARTMENT:	Department of Biosciences
AREA OF EXPERTISE:	Cell biology
SUPERVISOR:	Randi G. Syljuåsen
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DISSERTATION TITLE: *Targeting cancer cells through inhibition of cell cycle checkpoint kinases*

Targeting the DNA damage response to selectively kill cancer cells is a topic of great interest in the field of cancer research. Inhibitors of the cell cycle checkpoint kinases WEE1, CHK1 and ATR have been developed, and are currently in clinical trials for cancer treatment, as monotherapy or in combination with chemo- or radiation therapy. Although inhibition of these checkpoint kinases is a promising anti-cancer strategy, it will not be successful in all patients, because of the heterogeneous nature of cancer. Therefore, it is important to study the molecular mechanisms that underlie the cellular responses to the treatment. More knowledge is needed about which factors that contribute to sensitivity or resistance to checkpoint kinase inhibitors.

Sissel Hauge and colleagues have studied the cellular responses to inhibitors of the checkpoint kinases WEE1, CHK1 and ATR. It was shown that the p53 target protein p21 protects cancer cells from DNA damage and cell death after treatment with the WEE1 inhibitor MK1775 (AZD1775). Based on these results, p21 levels may be one factor to consider in the clinical implementation of WEE1 inhibitors. It was also demonstrated that combined inhibition of WEE1 and CHK1 caused a synergistic increase in S phase DNA damage followed by a synergistic decrease in cancer cell survival. Mechanistically, it was revealed that distinct functions of WEE1 and CHK1 in regulating replication initiation likely underlie the effects of the combination treatment. Furthermore, the results from the study were in line with previous work showing increased anti-cancer effects of combined WEE1 and CHK1 inhibition, supporting the notion that this combination could be an effective anti-cancer strategy. Finally, the combined inhibition of WEE1 and ATR was investigated. Results from this study showed increased DNA damage and decreased cancer cell survival after the combination treatment, and indicate that this combination could be a promising anti-cancer strategy for lung cancer.

In conclusion, these studies have given more knowledge about distinct functions of WEE1, CHK1 and ATR, and increased the insight into how inhibitors of these checkpoint kinases work to kill cancer cells.

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